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Baseline and long-term fibrinogen levels and risk of sudden cardiac death: a new prospective study and meta-analysis

Running Title: Fibrinogen and SCD

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Abstract

Background: Inflammatory markers such as C-reactive protein (CRP) and interleukin-6 have been linked with an increased risk of sudden cardiac death (SCD), but the relationship between fibrinogen and SCD is uncertain. We aimed to assess the association between fibrinogen and SCD.

Methods: Plasma fibrinogen was measured at baseline in a prospective cohort of 1773 men aged 42-61 years free of heart failure or cardiac arrhythmias that recorded 131 SCDs during 22 years follow-up. Correction for within-person fibrinogen variability was made using data from repeat measurements taken years apart.

Results: Fibrinogen was strongly correlated with CRP, weakly correlated with several cardiovascular risk markers, and was log-linearly associated with SCD risk. In analyses adjusted for conventional risk factors, the hazard ratio (HR) (95% CIs) for SCD per 1 standard deviation (SD) higher baseline log_e fibrinogen was 1.32 (1.11-1.57). The results remained consistent on further adjustment for alcohol consumption, resting heart rate, and circulating lipids 1.30 (1.09-1.56). The corresponding HRs were 1.80 (1.25-2.58) and 1.74 (1.20-2.52) after correction for within-person variability. HRs remained unchanged on further adjustment for CRP and accounting for incident coronary events. In a meta-analysis of three cohort studies, the fully-adjusted relative risks for SCD per 1 SD higher baseline and long-term fibrinogen levels were 1.42 (1.25-1.61) and 2.07 (1.59-2.69) respectively. The associations were similar for non-SCDs in both cohort analysis and the meta-analysis. Addition of plasma fibrinogen to a SCD risk prediction model containing established risk factors did not significantly improve risk discrimination, but improved the net reclassification.

Conclusions: Available data suggest fibrinogen is positively, log-linearly, and independently associated with risk of SCD. Further research is needed to assess the potential relevance of plasma fibrinogen concentrations in SCD prevention.

Keywords: fibrinogen; inflammation; sudden cardiac death; non-sudden cardiac death; regression dilution

1. Introduction

Sudden cardiac death (SCD) is a common manifestation of coronary heart disease (CHD) in the general population and is a global public health problem accounting for 15-20% of all deaths.^{1,2} Over the past decades, there has been a progressive decline in CHD due to major advances in treatment and preventive measures; in contrast, SCD rates have declined to a lesser extent.³ Though atherosclerotic cardiovascular disease (CVD) risk factors explain a large proportion of the risk for SCD,^{4,5} its pathogenesis is still not fully established. This emphasizes the need to better understand the epidemiology of SCD and evaluate the relevance of other potential risk factors.

Inflammation plays a central role in the development and progression of atherothrombosis.⁶ Emerging evidence indicates that inflammation may also be linked to the risk of SCD. Cardiac rhythm disturbances (particularly ventricular arrhythmias) are considered to be the leading events behind SCDs from atherothrombotic occlusion of coronary arteries;⁷ and inflammation has also been implicated in the pathogenesis of cardiac arrhythmias.⁸ Systemic markers of inflammation such as C-reactive protein (CRP), albumin, and interleukin-6 (IL-6) have been demonstrated to be associated with SCD in the general population.⁹⁻¹² Fibrinogen, an inflammatory marker, a major coagulation protein in the blood, and an important determinant of blood viscosity and platelet aggregation,^{13,14} is a risk factor for vascular events¹⁵ and has been demonstrated to be linked to cardiac arrhythmias;¹⁶ however, its association with SCD is uncertain. A number of studies have reported on the associations of fibrinogen with SCD in angina patients,^{17,18} but only two prospective studies have so far reported on the associations between baseline plasma fibrinogen levels and SCD risk in apparently healthy participants and their results have been inconsistent. Whereas one study showed a positive association,¹¹ the other study found no association,⁹ giving rise to uncertainty regarding the nature of the association. Out-of-hospital SCD is an unrecognized yet major contributor to SCDs, however, no study has at yet assessed the association of

fibrinogen with out-of-hospital SCDs. Finally, the long-term relevance of fibrinogen to SCD is unknown. This is particularly important, given that fibrinogen has been shown to exhibit high within-person variability¹⁹ as a result of measurement errors, fluctuations due to acute phase reactions, lifestyle changes, and chronic disease.²⁰ Given the established role of inflammation in the development of CHD, we hypothesized that elevated levels of plasma fibrinogen may be independently associated with an increased risk of SCD in the general population. Against this background, we aimed to evaluate in detail the nature and magnitude of the prospective association of fibrinogen with risk of SCD (in- and out-of-hospital SCDs) in a population-based cohort of 1773 apparently healthy men from eastern Finland. Repeat measurements of fibrinogen were performed 4 and 11 years after the baseline measurements in 959 participants to help quantify within-person variability in fibrinogen levels. To put our results into perspective, we also examined the association of fibrinogen with non-SCD. Finally, to contextualize the associations, we also performed a pooled analysis of the available prospective evidence on the associations.

2. Methods

2.1. Participants

The study population comprised of a representative sample of men living in the city of Kuopio and its surrounding rural communities in eastern Finland. Subjects were participants in the Kuopio Ischaemic Heart Disease (KIHD) risk factor study, a population-based prospective cohort study designed to investigate risk factors for CVD and related outcomes.²¹ Of the 3433 randomly selected men who were potentially eligible, 2682 (78%) volunteered to participate in the study. Participants were 42-61 years of age during baseline examinations performed between March 1984 and December 1989. For the present analyses, men with a prevalent history of heart failure or cardiac arrhythmias were excluded leaving a final cohort of 1773 men with non-missing information on plasma fibrinogen, relevant covariates, and

SCD outcomes. The Research Ethics Committee of the University of Eastern Finland approved the KIHHD study, and each participant gave written informed consent.

2.2. Ascertainment of outcomes

In the KIHHD study, participants are under continuous surveillance for the development of new CVD events, including incident cases and deaths.²² There were no losses to follow-up and all SCDs that occurred from study enrollment through 2012 were included. The sources of information on SCD outcomes were based on a comprehensive review of all available hospital records, wards of health centres, informant interviews, health practitioner questionnaires, medico-legal reports, and death certificate registers. Deaths were coded according to ICD-9 codes or ICD-10 codes. The diagnostic classification of SCDs was based on symptoms, electrocardiographic findings, cardiac enzyme elevations, autopsy findings (80% of all cardiac deaths), and history of CHD together with the clinical history and findings from hospital and paramedic staff. A death was determined to be an SCD when it occurred within 1 hour of the onset of an abrupt change in symptoms or within 24 hours after the onset of symptoms; including nonwitnessed cases when clinical and autopsy findings did not reveal a non-cardiac cause of sudden death or after successful resuscitation from ventricular tachycardia and/or ventricular fibrillation.²³ The witnessed subject was to have been seen alive and symptom free within 1 hour before the event. Sudden cardiac deaths that occurred in out-of-hospital conditions were also defined as events that occurred in places that had been reported accurately in hospital documents.²³ Documents were cross-checked in detail by two physicians. Non-SCDs were also carefully documented using standardized criteria. Cardiac deaths that did not lead to death during the following 24 hours of the onset of symptoms were considered as non-SCDs. The Independent Events Committee, masked to clinical data, performed classification of deaths.

2.3. Measurement of risk factors

Collection of blood specimens, data on socio-demographics, physical measurements, vascular risk factors, and the measurement of serum lipids and glucose have been described previously.²⁴ In addition to an overnight fast, participants were instructed to abstain from drinking alcohol for at least three days and from smoking for at least 12 hours prior to assessment. Blood samples were taken between 08:00 and 10:00 hours following rest in the supine position for 30 minutes. The serum samples were stored frozen at -80 °C for 0.2-2.5 years. Plasma fibrinogen concentrations were determined in fresh plasma samples with excess thrombin using the Coagulometer KC4 device (Heinrich Amelung GmbH, Lemgo, Germany). The coefficient of variation describing the day-to-day measurement of variability for fibrinogen assays was 5.5 percent. Repeat measurements of fibrinogen were performed 4 years and 11 years after baseline during a 22 year period in a random subset of participants. C-reactive protein (CRP) was measured with an immunometric assay (Immulite High Sensitivity C-Reactive Protein Assay; DPC, Los Angeles, CA, USA). History of diabetes was defined as having a clinical diagnosis of diabetes and regular treatment with diet, oral hypoglycaemic agents or insulin therapy, fasting plasma glucose ≥ 7.0 mmol/l, or according to self-reports. Standard resting 12-lead ECG was also recorded. The ECG criterion for left ventricular hypertrophy (LVH) was based on either the Sokolow-Lyon or Romhilt-Estes point score.²⁵⁻²⁸

2.4. Statistical analyses

Prospective cohort analyses Values of skewed variables were log-transformed to achieve approximately symmetrical distributions. We performed descriptive analyses summarising the baseline characteristics of the participants. Cross-sectional associations of fibrinogen with various risk markers were assessed using calculated partial correlation coefficients (adjusted for age). All analyses were conducted using Cox proportional hazard models. The proportional hazards assumptions were tested as previously described and satisfied.²⁹ To quantify and correct for within-person variability in levels of fibrinogen, that is, the extent to which an individual's fibrinogen measurements vary around a long-term

average level exposure (“usual levels”),¹⁹ adjusted regression dilution ratios (RDRs) were estimated by regressing available repeat measurements on baseline values.³⁰ The RDR assumed that the “usual levels” of fibrinogen represented the true long-term exposure of fibrinogen levels on SCD risk.³¹ To characterize shapes of associations, hazard ratios (HRs) were calculated within quartiles of baseline fibrinogen levels relative to the bottom quartile and plotted against mean fibrinogen levels in each quartile using floating absolute risks.³² As the association showed a log-linear shape, HRs were calculated per 1 standard deviation (SD) higher \log_e fibrinogen levels. The SD of baseline \log_e fibrinogen was 0.18 (equivalent to approximately one-fold higher circulating fibrinogen, as $e^{0.18}=1.19$). Hazard ratios were adjusted for age, BMI, systolic blood pressure (SBP), prevalent CHD, smoking status, history of diabetes mellitus, LVH, history of hypertension, use of medications (antihypertensive agents and lipid-lowering drugs), alcohol consumption, resting heart rate, triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and CRP. Formal tests of interaction were used to assess statistical evidence of effect modification by pre-specified clinically relevant characteristics, such as age at survey, BMI, SBP, CRP, history of diabetes, smoking status, history of hypertension, history of CHD, and use of anti-hypertensive agents. To avoid including cases with prevalent but undetected CHD, heart failure, and cardiac arrhythmias (which are direct causes of SCD), sensitivity analysis involved excluding the first five years of follow-up. To assess whether adding information on plasma fibrinogen measurements to documented established risk factors is associated with improvement in prediction of SCD risk, we calculated measures of discrimination for censored time-to-event data (Harrell’s C-index³³) and reclassification (the continuous net-reclassification-improvement [NRI], a category-free version of the NRI).³⁴ Measures of discrimination and reclassification were assessed for the risk model (age, SBP, cigarette smoking, serum low density lipoprotein cholesterol, history of diabetes, BMI, previous myocardial infarction, and family history of CHD) as previously described.^{23, 35}

Meta-analysis We conducted a meta-analysis of published studies reporting on the association between fibrinogen and SCD. Prospective (cohort or nested case-control) studies of the association

between fibrinogen and SCD that were published up to September 2015 were sought using computer-based databases (MEDLINE, EMBASE, and Science Citation Index). The computer-based searches combined free and MeSH search terms and combined key words related to fibrinogen (e.g., “fibrinogen”, “inflammation”) and sudden cardiac death (e.g., “sudden cardiac death”, “cardiac death”). There were no restrictions on language or the publication date. The details of the search strategy are presented in **Appendix Supplement 1**. The relative risk (RR) with 95% CIs was used as the summary measure of association across studies. To enable a consistent approach to the meta-analysis and enhance comparability, reported study-specific RRs were also transformed to per 1SD change in baseline fibrinogen values using standard statistical methods^{36, 37} which have been described in detail previously.^{38, 39} Associations of usual levels of fibrinogen and SCD were estimated using the correction factor derived from the KIID Study. The summary RR (including the estimate from the present study) was calculated using fixed effects meta-analysis. Statistical heterogeneity across studies was quantified using standard chi-square tests and the I^2 statistic.⁴⁰ All statistical analyses were conducted using Stata version 14 (Stata Corp, College Station, Texas).

3. Results

3.1. Baseline characteristics and correlates of fibrinogen

Table 1 summarizes baseline characteristics of the 1773 participants in the present study. Mean (SD) \log_e fibrinogen concentration was 1.09 (0.18) g/l. During an average follow-up of 22 years, there were 131 SCDs (annual rate 3.35/1,000 person-years at risk; 95% CI: 2.83 to 3.98). Of the total SCDs, 101 occurred out-of-hospital. Plasma fibrinogen levels were weakly and positively correlated with questionnaire and physical measures (age, alcohol consumption, BMI, blood pressure, and resting heart rate) and with several lipid and metabolic markers. A strong positive correlation was observed for \log_e CRP ($r = 0.55$) and weak inverse correlations observed for HDL-C ($r = -0.10$) and creatinine ($r = -0.12$). Baseline fibrinogen concentrations were higher in people with diabetes compared with people without

diabetes and higher in current smokers compared with non-smokers (**Table 2**).

3.2. Correction for within-person fibrinogen variability

Repeat measurements of fibrinogen taken 4 years and 11 years after baseline over 22 years were available in a random sample of 959 men, providing a total of 1,277 repeat measurements of fibrinogen. Overall, the RDR of \log_e fibrinogen, adjusted for age, was 0.48 (95% CI: 0.41 to 0.55), suggesting that the associations using one-off or baseline measurements of fibrinogen with SCD will be about half as strong as they otherwise would be using usual levels of fibrinogen. The within-person variability of fibrinogen was comparable to what has been previously reported.¹⁹

3.3. Fibrinogen and risk of sudden cardiac death

Prospective cohort analysis Cumulative hazard curves demonstrated a greater risk of new-onset SCDs among males in the top quartile of fibrinogen levels compared to those in the bottom quartile (P for log-rank test= 0.0001; **Figure 1**). Baseline and usual fibrinogen levels were log-linearly associated with risk of SCD in analyses adjusted for conventional risk factors (age, BMI, SBP, prevalent CHD, smoking status, history of diabetes mellitus, LVH, history of hypertension, use of antihypertensive agents and lipid-lowering drugs) and potential confounders (alcohol consumption, resting heart rate, triglycerides, total cholesterol, HDL-C, and CRP) (**Figures 2-3**). The age-adjusted HR per 1 SD change in baseline \log_e fibrinogen level was 1.59 (95% CI: 1.36 to 1.87; $P < 0.001$), which was attenuated following further adjustment for conventional risk factors 1.32 (95% CI: 1.11 to 1.57; $P = 0.002$). The results remained consistent on further adjustment for several potential confounders 1.30 (95% CI: 1.09 to 1.56; $P = 0.004$). The corresponding HRs per 1 SD change in usual \log_e fibrinogen levels were 2.64 (95% CI: 1.89 to 3.70; $P < 0.001$), 1.80 (95% CI: 1.25 to 2.58; $P = 0.002$), and 1.74 (95% CI: 1.20 to 2.52; $P = 0.004$) respectively. The HRs remained unchanged after further adjusting for CRP and accounting for incident coronary events (**Table 3**). The HR for SCD per 1 SD change in baseline \log_e fibrinogen level in age-

adjusted analysis was 1.59 (95% CI: 1.36 to 1.87; $P < 0.001$), which was minimally attenuated after single adjustment for prevalent CHD 1.53 (95% CI: 1.30 to 1.80; $P < 0.001$) and remained unchanged on further adjustment for incident coronary events 1.50 (95% CI: 1.28 to 1.77; $P < 0.001$). HRs did not vary importantly by levels or categories of pre-specified conventional risk factors (**Figure 4**), and the main results remained the same in analyses that excluded the first five years of follow-up (data not shown). To put the strength of the association of fibrinogen with risk of SCD into context, comparisons were made to associations of fibrinogen with acute myocardial infarction (AMI) and ventricular arrhythmias (VAs). The initial positive association of fibrinogen with risk of AMI in analyses adjusted for several established and emerging risk factors was attenuated on further adjustment for CRP. There was no statistically significant evidence of an association with VAs (**Appendix Supplement 2**). Addition of CRP measurements alone to a SCD risk prediction model increased the C-index significantly by 0.0171 (95% CI: 0.0037 to 0.0304; $P=0.012$) and yielded a NRI of 37.7% (10.9 to 64.4%, $P=0.006$). When information on plasma fibrinogen measurements alone was added to the prediction model, the C-index change was 0.0128 (-0.0063 to 0.0319; $P=0.188$) and NRI was 54.6% (28.4 to 80.9%, $P<0.001$). On addition of information on both CRP and fibrinogen measurements to the model, the C-index increased significantly by 0.0140 (0.0006 to 0.274; $P=0.041$) and the NRI was 33.1% (7.4 to 58.7%, $P=0.011$).

In separate analyses for out-of-hospital SCDs, the initial positive association of fibrinogen with out-of-hospital SCDs in age-adjusted analyses was less robust upon further adjustment for established risk factors and potential confounders, however, became stronger with further adjustment for CRP.

For non-SCDs, the age-adjusted HR per 1 SD change in baseline \log_e fibrinogen level was 1.61 (95% CI: 1.26 to 2.04; $P < 0.001$), which was attenuated following further adjustment for conventional risk factors 1.41 (95% CI: 1.09 to 1.84; $P = 0.010$). The results remained consistent on further adjustment for several potential confounders, CRP, and accounting for incident coronary events 1.39 (95% CI: 1.02 to 1.91; $P = 0.039$) (**Table 3**).

Literature-based meta-analysis Including the current study, we identified three population-based prospective studies reporting on the associations between plasma fibrinogen and risk of SCDs and non-SCDs (**Appendix Supplement 3**).^{9, 11} In pooled fixed effects analysis involving 25 553 participants and 388 SCD events, the RRs for SCD per 1 SD higher baseline and usual fibrinogen levels, typically adjusted for several conventional and potential risk factors for SCD were 1.42 (95% CI: 1.25 to 1.61; $P < 0.001$) and 2.07 (95% CI: 1.59 to 2.69; $P < 0.001$) respectively ($I^2=2.0\%$, 95% CI: 0-90%; $P=0.359$) (**Appendix Supplement 4**). For pooled analysis of 269 non-SCDs, the corresponding RRs were 1.40 (95% CI: 1.21 to 1.63; $P < 0.001$) and 2.02 (95% CI: 1.47 to 2.76; $P < 0.001$), with no evidence of heterogeneity between studies (**Appendix Supplement 5**).

4. Discussion

4.1. Key findings

Our findings in the KIID cohort comprising middle-aged to older men without a history of HF or cardiac arrhythmias at baseline, provide several relevant findings that have not been previously reported. Indeed, fibrinogen was strongly correlated with CRP as expected and there were generally weak associations with several cardiovascular risk markers. In analyses adjusted for several established and emerging risk factors, we observed log-linear associations of baseline and usual levels of fibrinogen with risk of SCD. The association did not materially change on further adjustment for a comprehensive panel of potential confounders and remained consistent on additional adjustment for CRP. The fibrinogen-SCD association remained materially unchanged after adjusting for prevalent CHD and incident coronary events in analysis initially only adjusted for age. The overall findings remained generally consistent (albeit imprecise estimates for the categories with lower event rates) across several subgroups and levels of cardiovascular risk markers. The associations were similar for non-SCDs. Our finding of a significant evidence of an association of fibrinogen with SCD is consistent with a previous report from the Atherosclerosis Risk in Communities (ARIC) study,¹¹ but in contrast to the lack of an association

observed in the the Etude PRospective de l'Infarctus du Myocarde (PRIME) study.⁹ Differences in statistical power may explain the apparently contradictory results. There was a lower event rate in the PRIME study (50 SCDs) compared to our study and that of the ARIC study. A significant association with out-of-hospital SCDs was observed in age-adjusted analyses, but was attenuated after adjustment for established risk factors. There was a negative confounding effect of CRP on the association which was not expected, given the strong positive correlation of fibrinogen with CRP. Furthermore, pooled analysis of risk estimates from the three studies (including ours) reinforce the validity and generalizability of these new data. Finally, our analyses indicate that addition of information on plasma fibrinogen measurements to risk factors for SCD did not incrementally improve SCD risk prediction, but yielded a significant improvement in reclassification.

4.2. Possible explanations for findings

The current findings highlight and lend further support to the inflammatory hypothesis involved in the development of CHD, the major pathology underlying SCD. Indeed, pathological signs of inflammation have been demonstrated in the coronary atherosclerotic lesions which are found in majority of cases of SCD.^{41,42} This inflammatory hypothesis has also been evaluated in several population-based cohort studies and it has been demonstrated that systemic inflammatory markers such as CRP, IL-6, albumin, and white blood cell counts are robustly associated with SCDs.^{9-11,43} However, our observed fibrinogen-SCD association remained robust after adjusting for CRP (the most commonly used marker of low-grade chronic inflammation), which supports the hypothesis that other pathways apart from inflammatory processes may also play a role in the etiology between fibrinogen and SCDs. In our study, we observed that the significant association of fibrinogen with AMI was attenuated on further adjustment for CRP, which also reflects the possibility that inflammatory mechanisms mainly underlie the etiological association between fibrinogen and CHD, but not between fibrinogen and SCD. In line with the coagulative properties of fibrinogen in blood and it being an important determinant of blood viscosity and

platelet aggregation,^{13, 14} other potential pathways have been postulated. These include endothelial injury,¹⁷ the formation of low permeability fibrin clot in association with elevated fibrinogen levels,⁴⁴ thrombosis,⁴⁵ abnormalities of blood flow,⁴⁶ platelet hyperactivity,⁴⁷ and the contribution of fibrinogen to the development of subclinical atherosclerosis which eventually leads to SCD.^{10, 48} Additionally, it has been suggested that fibrinogen may contribute directly to the onset of arrhythmias, which often lead to SCD in the presence of underlying CHD.^{5, 49} The involvement of fibrinogen in arrhythmogenesis has been attributed to pathways associated with the inflammatory cascade and hemodynamic alterations.^{50, 51} Fibrinogen may also cause acute myocardial ischemia, which is the most common trigger for fatal arrhythmias.⁵² Our study, however, did not demonstrate any statistically significant evidence of an association between fibrinogen and VAs, which may be attributed to the low event rate.

Collectively, the present study establishes a robust observational association between fibrinogen and SCD risk. Although this does not establish causality, the linear and independent relationship is suggestive of causality. Establishing causality will require research designs that can minimize potential residual biases, such as rigorous randomized controlled trials of selective fibrinogen-lowering agents or Mendelian randomisation (MR) studies of genetic variants specifically related to fibrinogen levels.⁵³

4.3. Implications of findings

Our findings demonstrate a clear and independent link between plasma fibrinogen and SCD risk, which may have potential clinical implications. Our findings of no incremental improvement in SCD prediction on addition of information on plasma fibrinogen to a risk prediction score, does not rule out the potential for fibrinogen assays to be used in the identification of individuals at high risk for SCD. There was a net reclassification improvement and our risk prediction analyses were limited as we did not have complete measurements on several risk factors (e.g., ECG parameters, measures of heart rate variability, measures of ejection fraction, and angiographic findings) used in standard risk prediction algorithms for SCD.⁵⁴⁻⁵⁷ Given the robust and independent long-term association demonstrated between baseline levels

of fibrinogen and risk of SCD and the ease and simplicity of measuring fibrinogen assays, plasma fibrinogen remains a promising though unproven strategy for SCD risk prevention and its potential usefulness in SCD risk prediction deserves further investigation. Although the causal nature of the fibrinogen-SCD association has not been established, there remains a possibility that lowering or modification of plasma levels of fibrinogen may decrease the risk of future SCD, given that plasma fibrinogen levels can be considerably reduced by lifestyle interventions such as regular exercise and smoking cessation, which also affect levels of established vascular risk factors.¹⁵ Our reproducibility substudies of fibrinogen measurements in the KIID study and findings from the Fibrinogen Studies Collaboration¹⁹ indicate a high within-person variability in fibrinogen levels. This suggests that analyses using only single baseline measurements of fibrinogen underestimates the associations substantially as we have demonstrated. The poor reproducibility of fibrinogen may therefore limit its utility as a reliable risk indicator in clinical practice based on just a single baseline measurement. Formal risk assessment analyses involving large-scale individual participant data are warranted to assess the potential clinical utility of fibrinogen as a risk assessment tool for SCD.

4.4. Strengths and limitations

We had the advantage of a large sample that was selected to be a nationally representative population-based sample of middle-aged men, was well characterised, involved high response rates and there were no losses during follow-up. Participants have been prospectively and annually monitored using established hospital databases and supplemented with reliable data on a comprehensive panel of lifestyle and biological markers to allow adequate adjustment for potential confounding. The mean follow-up period was sufficiently long to ascertain the risk for SCD in the general population. Serial measurements of fibrinogen made within a subset of individuals over time were available, enabling quantification of the extent of within-person variability over the long period of follow-up. All previous epidemiological studies on fibrinogen and SCD risk were not able to correct for fibrinogen variability, potentially yielding biased

estimates. The KIID study made such a correction on the basis of two repeated measurements, indicating an independent association of fibrinogen with SCD. The reliability of the data was also confirmed by our ability to replicate the independent association of fibrinogen with non-SCD.^{9, 11} Another limitation was the small number of SCD events. Though repeat measurements of fibrinogen several years apart enabled correction for long-term within-person variability, we were unable to account for short-term variability, such as seasonal or diurnal fluctuations.^{58, 59} In addition, repeat measurements of fibrinogen were only made within a subset of men; therefore studies are needed with repeat measurements of fibrinogen in larger numbers of participants to assess fibrinogen variability in greater detail. Considering that fibrinogen levels were correlated with the several established and emerging risk factors we adjusted for and the fact that we only had repeat measurements of fibrinogen, there is a possibility of biases in either direction for our observed association between long-term average levels of fibrinogen and SCD.⁶⁰ However, this is unlikely for the following reasons: i) with the exception of the strong correlation with CRP, fibrinogen was weakly correlated with several established and emerging risk factors, which suggests the scope for minimal confounding for the association as we have demonstrated and ii) after adjustment for established risk factors, the association remained essentially consistent following additional adjustment for several potential confounders such as lipids and CRP. Though we adjusted for a comprehensive panel of confounders, there is still a possibility of potential residual confounding due to errors in risk marker measurements and other unmeasured confounders [such as IL-6, white blood cell counts, von Willebrand factor, class of anti-hypertensives, and use of anti-inflammatory drugs (e.g. aspirin), anticoagulants (e.g., warfarin), or hypoglycemic agents]. We also acknowledge that the study included only relatively middle-aged Caucasian men and therefore the associations demonstrated cannot necessarily be extrapolated to older men (> 61 years), women and other ethnicities. This is particularly important as fibrinogen exhibits considerable variability within individuals over time as a result of the dynamics of lifestyle factors as well as ageing.²⁰ Finally, the limited number of studies for the meta-analysis precluded the ability to adequately quantify heterogeneity (evidenced by the wide confidence

intervals for heterogeneity estimates) and explore this between contributing studies. Additional larger-scale prospective studies with relevant data may be needed to confirm our findings.

5. Conclusions

Available data suggest fibrinogen is positively, log-linearly, and independently associated with future risk of SCD in the general male population. Further research is needed to replicate these findings and assess the potential relevance of plasma fibrinogen concentrations in SCD prevention.

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Conflicts of Interest

None.

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Table 1. Baseline participant characteristics

	Overall (N=1773) Mean (SD) or median (IQR) OR n (%)	Without SCD (N=1642) Mean (SD) or median (IQR) or n (%)	With SCD (N=131) Mean (SD) or median (IQR) n (%)	P-value
Fibrinogen (g/l)	2.96 (2.62-3.32)	2.93 (2.61-3.30)	3.19 (2.87-3.57)	< 0.0001
<i>Questionnaire/Prevalent conditions</i>				
Age at survey (years)	52.3 (5.3)	52.3 (5.3)	53.7 (4.2)	0.002
Alcohol consumption (g/week)	76.8 (144.2)	75.3 (144.9)	95.3 (134.9)	0.126
History of diabetes	82 (4.6)	69 (4.2)	13 (9.9)	0.003
Current smokers	562 (31.7)	500 (30.5)	62 (47.3)	< 0.001
Left ventricular hypertrophy	20 (1.1)	19 (1.2)	1 (0.8)	0.681
History of hypertension	506 (29)	465 (28.3)	41 (31.3)	0.468
History of CHD	373 (21.0)	321 (19.6)	52 (39.7)	< 0.001
Use of anti-hypertensives	319 (18.0)	283 (17.2)	36 (27.5)	0.003
Medication for dyslipidemia	10 (0.6)	10 (0.6)	0 (0.0)	0.370
<i>Physical measurements</i>				
BMI (kg/m ²)	26.9 (3.5)	26.8 (3.4)	28.0 (4.3)	0.0001
SBP (mmHg)	133.7 (16.3)	133.4 (16.1)	137.9 (17.3)	0.002
DBP (mmHg)	89.2 (10.4)	89.0 (10.4)	91.2 (10.2)	0.023
Resting heart rate (bpm)	62.4 (10.7)	62.3 (10.6)	64.0 (11.7)	0.069
<i>Lipid markers</i>				
Total cholesterol (mmol/l)	5.91 (1.08)	5.89 (1.08)	6.16 (1.12)	0.006
HDL-C (mmol/l)	1.29 (0.30)	1.29 (0.30)	1.23 (0.26)	0.022
Triglycerides (mmol/l)	1.10 (0.80-1.55)	1.09 (0.79-1.52)	1.13 (0.85-1.63)	0.034
<i>Metabolic and inflammatory markers</i>				
Fasting plasma glucose (mmol/l)	5.32 (1.23)	5.29 (1.16)	5.69 (1.87)	0.0004
Serum creatinine (μmol/l)	89.2 (13.4)	89.5 (13.3)	85.7 (13.2)	0.0026
CRP (mg/l)	1.22 (0.69-2.25)	1.19 (0.67-2.18)	1.74 (0.92-3.09)	0.0001

BMI, body mass index; CHD, coronary heart disease; CRP, C-reactive protein; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; SD, standard deviation; SBP, systolic blood pressure; SCD, sudden cardiac death

Table 2. Cross-sectional correlates of fibrinogen

	Pearson correlation r (95% CI)†	Percentage difference (95% CI) in fibrinogen levels per 1 SD higher or compared to reference category of correlate‡
Log _e fibrinogen (g/l)	-	-
Questionnaire/Prevalent conditions		
Age at survey (yrs)	0.16 (0.11, 0.20)***	3% (2, 4)***
Alcohol consumption (g/week)	0.12 (0.08, 0.17)***	2% (1, 3)***
History of diabetes		
No	-	Ref
Yes	-	6% (2, 11)*
Smoking status		
Other	-	Ref
Current	-	12% (11, 14)***
Left ventricular hypertrophy		
No	-	Ref
Yes	-	8% (-1, 17)
History of hypertension		
No	-	Ref
Yes	-	1% (-0, 3)
History of CHD		
No	-	Ref
Yes	-	5% (3, 7)***
Use of anti-hypertensives		
No	-	Ref
Yes	-	3% (1, 6)*
Medication for dyslipidemia		
No	-	Ref
Yes	-	10% (-2, 23)
Physical measurements		
BMI (kg/m ²)	0.12 (0.07, 0.16)***	2% (1, 3)***
SBP (mmHg)	0.03 (-0.01, 0.08)*	1% (-0, 1)
DBP (mmHg)		
Resting heart rate (bpm)	0.09 (0.05, 0.14)***	2% (1, 3)***
Lipid markers		
Total cholesterol (mmol/l)	0.11 (0.07, 0.16)***	2% (1, 3)***
HDL-C (mmol/l)	-0.10 (-0.15, -0.05)***	-2% (-3, -1)***
Log _e triglycerides (mmol/l)	0.10 (0.06, 0.15)***	2% (1, 3)***
Metabolic and inflammatory markers		
Fasting plasma glucose (mmol/l)	0.09 (0.05, 0.14)***	2% (1, 3)**
Serum creatinine (μmol/l)	-0.12 (-0.17, -0.07)***	-2% (-3, -1)***
Log _e C-reactive protein (mg/l)	0.55 (0.51, 0.58)***	10% (10, 11)***

BMI, body mass index; CHD, coronary heart disease; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; SD, standard deviation; SBP, systolic blood pressure; †Pearson correlation coefficients between log_e fibrinogen and the row variables; ‡, Percentage change in fibrinogen levels per 1-SD increase in the row variable (or for categorical variables, the percentage difference in mean fibrinogen levels for the category versus the reference) adjusted for age; asterisks indicate the level of statistical significance: *, p<0.05; **, p<0.01; ***, p<0.001

Table 3. Associations of baseline and usual fibrinogen levels with sudden cardiac deaths, out-of-hospital sudden cardiac deaths, and nonsudden cardiac deaths

Models	Sudden cardiac death		Out-of-hospital sudden cardiac death		Non-sudden cardiac death	
	Hazard ratio (95% CI)	<i>P</i> -value	Hazard ratio (95% CI)	<i>P</i> -value	Hazard ratio (95% CI)	<i>P</i> -value
	1773 participants and 131 cases		1773 participants and 101 cases		1773 participants and 61 cases	
Baseline fibrinogen						
Model 1	1.59 (1.36 to 1.87)	< 0.001	1.43 (1.19 to 1.73)	< 0.001	1.61 (1.26 to 2.04)	< 0.001
Model 2	1.32 (1.11 to 1.57)	0.002	1.20 (0.98 to 1.46)	0.076	1.41 (1.09 to 1.84)	0.010
Model 3	1.30 (1.09 to 1.56)	0.004	1.18 (0.97 to 1.45)	0.106	1.40 (1.08 to 1.83)	0.012
Model 4	1.32 (1.07 to 1.62)	0.010	1.28 (1.01 to 1.63)	0.040	1.42 (1.04 to 1.93)	0.027
Model 5	1.31 (1.06 to 1.62)	0.011	1.28 (1.01 to 1.62)	0.043	1.39 (1.02 to 1.91)	0.039
Usual fibrinogen						
Model 1	2.64 (1.89 to 3.70)	< 0.001	2.12 (1.43 to 3.13)	< 0.001	2.69 (1.63 to 4.43)	< 0.001
Model 2	1.80 (1.25 to 2.58)	0.002	1.45 (0.96 to 2.20)	0.076	2.06 (1.19 to 3.55)	0.010
Model 3	1.74 (1.20 to 2.52)	0.004	1.42 (0.93 to 2.16)	0.106	2.03 (1.17 to 3.53)	0.012
Model 4	1.78 (1.15 to 2.74)	0.010	1.68 (1.02 to 2.75)	0.040	2.06 (1.09 to 3.92)	0.027
Model 5	1.76 (1.14 to 2.73)	0.011	1.67 (1.02 to 2.75)	0.043	1.99 (1.03 to 3.85)	0.039

Hazard ratios are reported per 1 standard deviation increase in log_e fibrinogen levels

Model 1: Adjusted for age

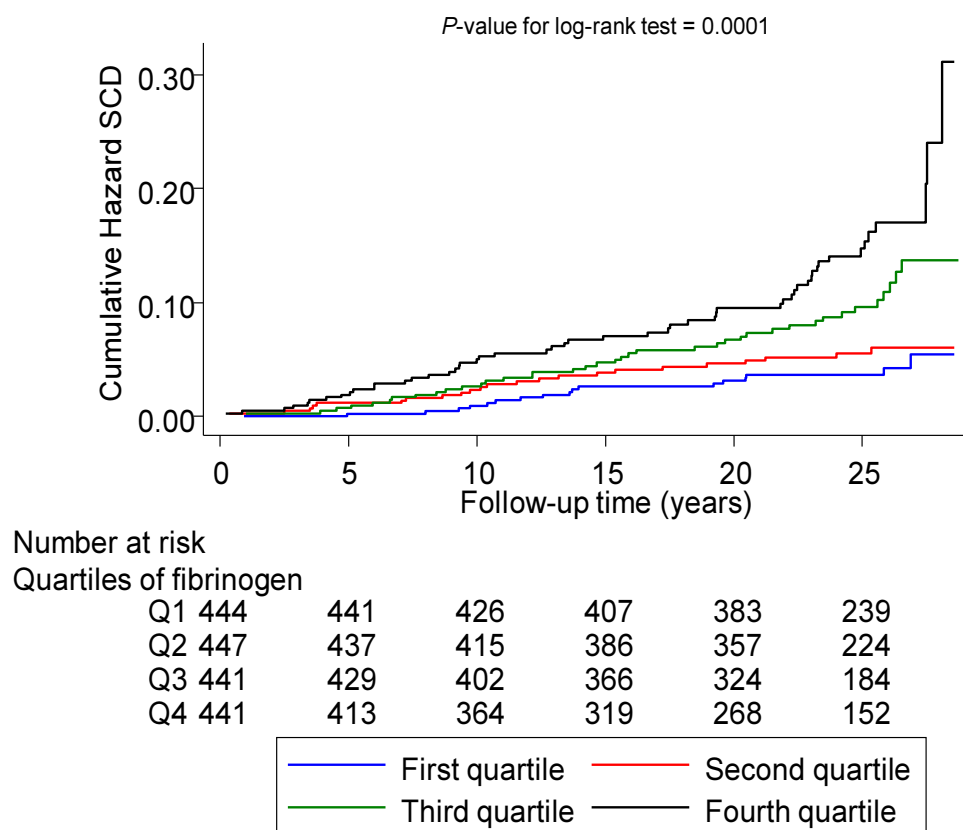
Model 2: Model 1 plus body mass index, systolic blood pressure, prevalent coronary heart disease, smoking status, history of diabetes, left ventricular hypertrophy, history of hypertension, and use of medications (antihypertensive agents and lipid-lowering drugs)

Model 3: Model 2 plus alcohol consumption, resting heart rate, triglycerides, total cholesterol, and high-density lipoprotein cholesterol

Model 4: Model 3 plus C-reactive protein

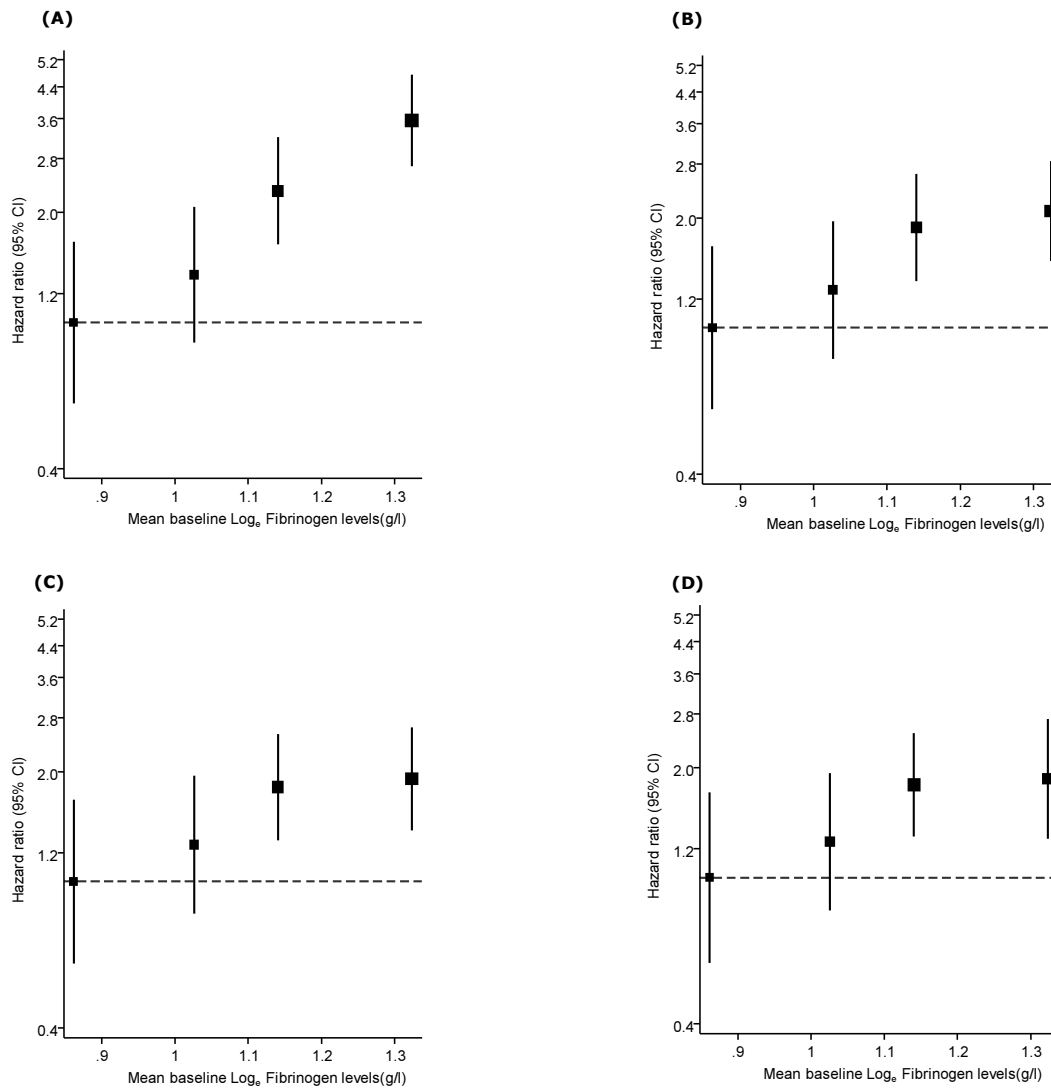
Model 5: Model 4 plus incident coronary heart disease as a time-dependent covariate

Figure 1. Cumulative hazard curves for sudden cardiac death by quartiles of fibrinogen



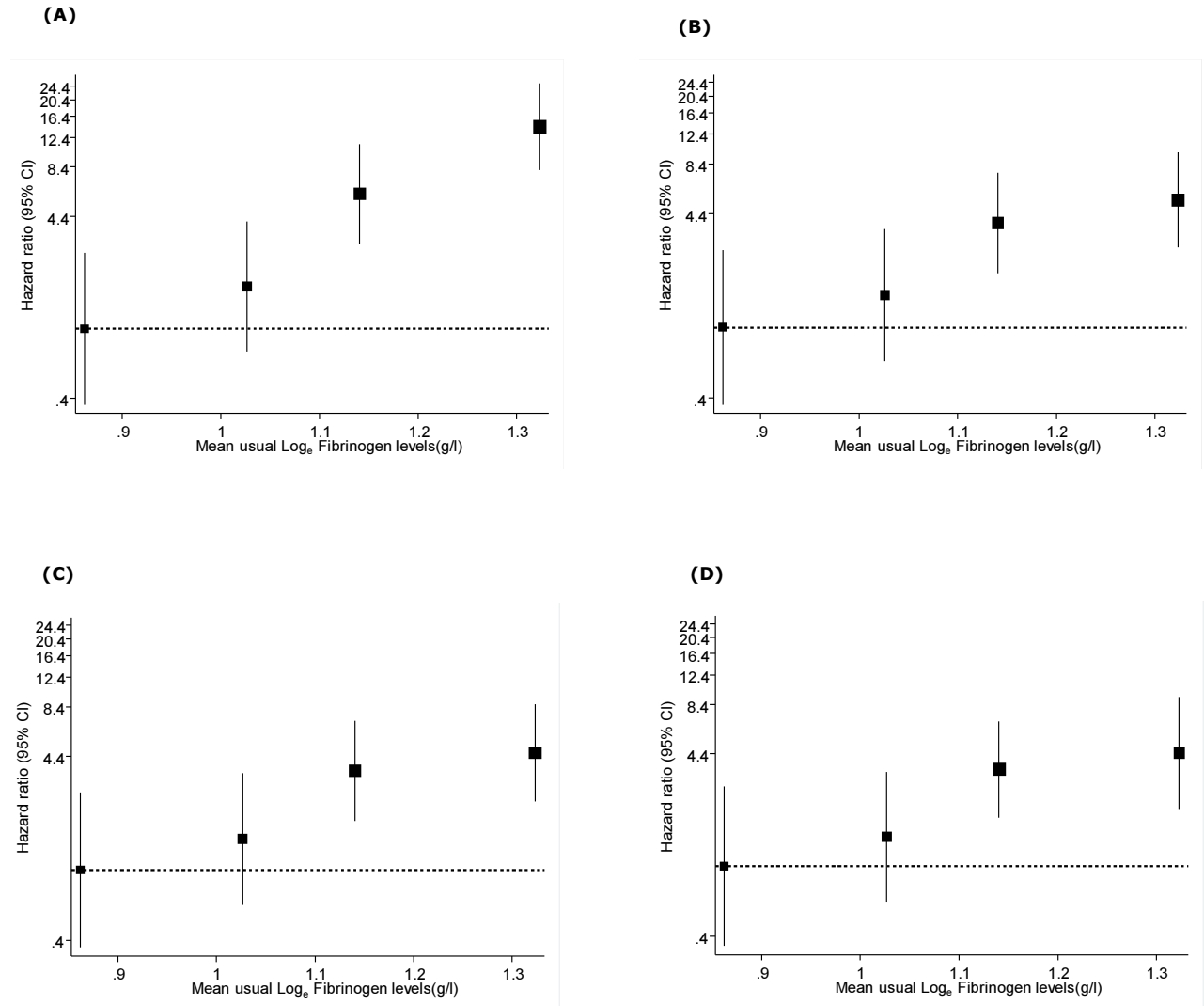
The median fibrinogen level (g/l) was 2.42 (range 1.78-2.62) for the lowest quartile; 2.79 (range 2.62-2.96) for the second quartile; 3.13 (range 2.96-3.32) for the third quartile; and 3.64 (range 3.33-5.96) for the top quartile; SCD, sudden cardiac death

Figure 2. Hazard ratios for sudden cardiac death, by quartiles of baseline levels of log_e fibrinogen



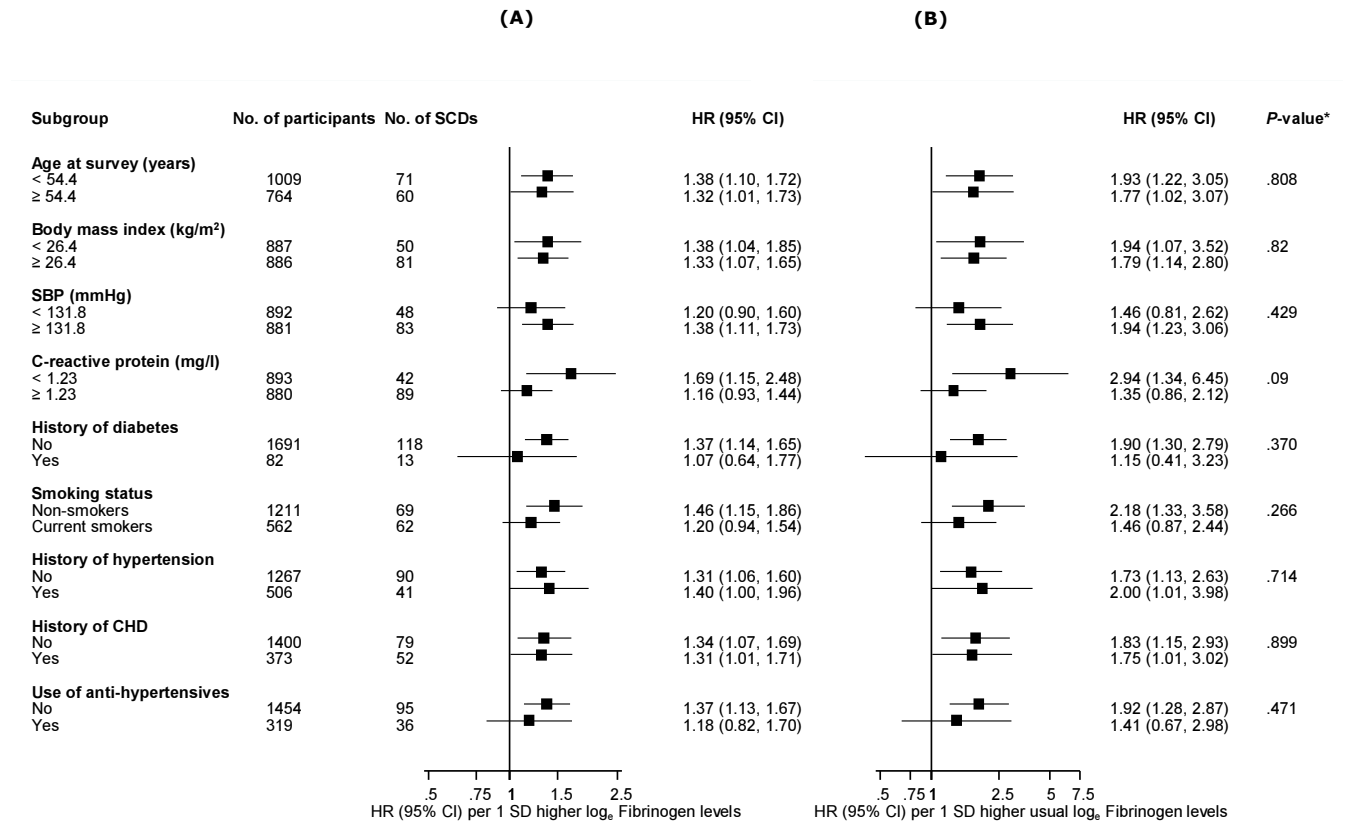
A, adjusted for age; **B**, adjusted for age, body mass index, systolic blood pressure, prevalent coronary heart disease, smoking status, history of diabetes, left ventricular hypertrophy, history of hypertension, and use of medications (antihypertensive agents and lipid-lowering drugs); **C**, adjusted for B plus alcohol consumption, resting heart rate, triglycerides, total cholesterol, and high-density lipoprotein cholesterol; **D**, adjusted for C plus C-reactive protein

Figure 3. Hazard ratios for sudden cardiac death, by quartiles of usual levels of log_e fibrinogen



A, adjusted for age; **B**, adjusted for age, body mass index, systolic blood pressure, prevalent coronary heart disease, smoking status, history of diabetes, left ventricular hypertrophy, history of hypertension, and use of medications (antihypertensive agents and lipid-lowering drugs); **C**, adjusted for B plus alcohol consumption, resting heart rate, triglycerides, total cholesterol, and high-density lipoprotein cholesterol; **D**, adjusted for C plus C-reactive protein

Figure 4. Hazard ratios for baseline and usual \log_e fibrinogen and sudden cardiac death risk by several participant level characteristics



A, baseline levels of fibrinogen; **B**, usual levels of fibrinogen; hazard ratios were adjusted for age, body mass index, systolic blood pressure, prevalent coronary heart disease, smoking status, history of diabetes, left ventricular hypertrophy, history of hypertension, and use of medications (antihypertensive agents and lipid-lowering drugs); CI, confidence interval; HR, hazard ratio; SCDs, sudden cardiac deaths; SD, standard deviation; SBP, systolic blood pressure; *, *P*-value for interaction; cut-offs used for age, body mass index, systolic blood pressure, and C-reactive protein are median values.